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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/997,585 | 11/15/2001 | Avi J. Ashkenazi | P2730P1C41 | 1273 |

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| EXAMINER | |
|---|---|
| DEBERRY, REGINA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/997,585 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Regina M. DeBerry | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

***Status of Application, Amendments and/or Claims***

The amendment filed 17 June 2004 has been entered in full. Claim 124 was cancelled. Claims 119-123 are under examination.

The information disclosure statement (IDS) filed 17 June 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The Declaration of Avi Ashkenazi under 37 CFR1.132 has been entered.

The Declaration of Paul Polakis under 37 CFR1.132 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Withdrawn Objections And/Or Rejections***

The rejection to claims 119 and 124 under 35 U.S.C. 112, second paragraph, as set forth at page 6 of the previous Office Action (18 March 2004) is *withdrawn* in view of the amendment (17 June 2004).

**35 U.S.C. §§ 101 and 112, First Paragraph**

Claims 119-123 remain rejected under 35 U.S.C. § 101 because the claimed invention is not supported by a specific and substantial asserted utility or a well established utility.

Claims 119-123 remain rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would clearly not know how to use the claimed invention.

The basis for these rejections is set forth at pages 2-6 of the previous Office Action (18 March 2004).

Applicant's arguments submitted in the response received 17 June 2004 have been fully considered but are not found to be persuasive for the following reasons. The Ashkenazi declaration and Polakis declaration under 37 CFR 1.132 filed 17 June 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons.

Applicant states that the Examiner acknowledged that the nucleic acids encoding PRO1187 showed a positive correlation for lung cancer. Applicant states that if the Applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art; do not impose a rejection based on the lack of utility. Applicant cites the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in MPEP 2107 II (B) in support of this assertion. Applicant urges that a *prima facie* case of lack of utility has not been established.

Applicants state that they rely on the gene amplification data for the patentable utility of this case. Applicant maintains that the claimed utility for the PRO1187 protein and its antibody is based on its use in the diagnosis of lung cancer and is not based on

structural similarity to known proteins. Applicant discusses the PRO1187 data. Applicant asserts that the PRO1187 gene has utility as a diagnostic marker.

Applicant's arguments have been carefully considered but are not found to be persuasive. Firstly, the Examiner stated, "while the specification **may have** utility for the polynucleotide, the instant claims are drawn to the polypeptide" (previous Office Action 18 March 2004, page 4). The Examiner **did not** acknowledge that the nucleic acid encoding PRO1187 showed a positive correlation for lung cancer. Secondly, the Examiner is not questioning whether the asserted utility is credible. The question is whether the asserted utility is specific and substantial.

The instant specification teaches that primary tumor (human lung tumor) LT12, LT15 and LT16 have delta ct units of 1.17, 1.55 and 1.33 respectively for PRO1187. The specification provides data showing a very small increase in DNA copy number, approximately 2-3 fold, in a few tumor samples for PRO1187. No evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer. There is no evidence regarding whether or not the **PRO1187 mRNA or protein levels** are also increased in these tumor samples (Emphasis added). Since the instant claims are directed to the antibody that binds PRO1187 protein, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and protein levels.

Applicant criticizes the Examiner's reliance on Haynes *et al.* (reference of record). Applicant states that Haynes *et al.* teach that there was a general trend, but no

strong correlation between protein expression and transcript levels. Applicant states that the Examiner bases her conclusion that increases in gene copy number do not reliably correlate with increase gene expression or polypeptide expression on Haynes *et al.* and hence concludes that PRO1187 polypeptides and their antibodies lack utility.

This has been fully considered but is not found to be persuasive. Pennica *et al.* was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka *et al.* was cited as evidence showing lack of correlation between gene amplification and increased protein levels. Haynes *et al.* was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (p. 1863). Haynes *et al.* used yeast as an art-accepted model for eukaryotic systems.

Applicant discusses the references submitted in the IDS to demonstrate that if a gene is amplified in cancer, it is more than likely than not that the encoded protein will be expressed at an elevated level. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Applicant refers to three articles (Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*) as providing evidence that gene amplification generally results in elevated levels of the encoded protein. Applicant characterizes Orntoft *et al.* as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman *et al.* as providing evidence of a prominent

global influence of copy number changes on gene expression levels. Applicant characterizes Pollack *et al.* as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels.

This has been fully considered but is not found to be persuasive. Orntoft *et al.* appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft *et al.* do not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1187 in the instant specification. That is, it is not clear whether or not PRO1187 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft *et al.* is not clear. Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman *et al.* also do not support utility of the claimed proteins. Pollack *et al.* also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate protein levels. Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention.

None of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1187 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Given how small the DNA copy number of PRO1187 increased, and the evidence provided by Haynes *et al.*, Pennica *et al.* and Konopka *et al.*, it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or protein levels. One skilled in the art would do further research to determine whether or not the PRO1187 protein levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

Applicant refers to the Polakis declaration, which asserts that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. The Polakis declaration asserts that antibodies to approximately 30 of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Applicant refers to the Ashkenazi

declaration, which asserts that if the protein levels do not increase as a result of gene amplification, it is also useful because it can serve to better diagnose the cancer and lead to a suitable therapy.

This has been fully considered but is not found to be sufficient to withdraw the rejection, since **there is no indication in the specification or in the declarations that the PRO1187 mRNA or protein levels increase or stay the same** (Emphasis added). The instant specification provides no information regarding increased mRNA levels of PRO1187 in tumor samples relevant to normal samples. Only gene amplification data was presented. The Polakis declaration is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the Examiner can independently draw conclusions, since only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu *et al.* (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu *et al.* discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation

between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Further research would be needed to determine PRO1187 mRNA and protein levels in cancers showing gene amplification of PRO1187 gene. The proposed use of the PRO1187 proteins as claimed in this application are simply starting points for further research and investigation into potential practical uses of the proteins and antibodies. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Therefore, the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, are maintained.

***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
9/16/04